

# Botulinum Toxin in Migraine Treatment

## Migren Tedavisinde Botulinum Toksini

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### ABSTRACT

Since botulinum toxin might have a therapeutic effect on pain, many studies investigating the efficiency of botulinum toxin in headache treatment have been done. The most satisfying results were achieved by botulinum toxin type A (BoNT/A) in the treatment of chronic migraine. In this paper, we reviewed the clinical effectiveness of BoNT/A in migraine and included our clinical experience. In our ongoing pilot study, where we have repeated BoNT/A injections every 12 weeks, The difference in the Migraine Disability Assessment (MIDAS) scores between the first and the second injections was 61.1%; and between the first and the 3rd injections was found to be 65.72%. (*Archives of Neuropsychiatry 2013; 50 Supplement 1: S36-S40*)

**Key words:** Botulinum toxin, chronic migraine, headache

**Conflict of interest:** The authors reported no conflict of interest related to this article.

### ÖZET

Botulinum toksininin ağrı kontrolünde de etkisi olabileceğinin farkedilmesi üzerine baş ağrısı tedavisindeki yararlılığını araştıran birçok çalışma yapılmıştır. Bu çalışmalarda en yüz güldürücü sonuçlar, Botulinum toksin A'nın (BoNT/A) kronik migrendeki kullanımında elde edilmiştir. Bu derlemede BoNT/A'nın migren profilaksisindeki etkinliğini, kendi klinik deneyimlerimizi de ilave ederek değerlendirdik. Kliniğimizde başlattığımız ve halen devam eden bir öncü çalışmada 12 hafta aralıklarla değerlendirdiğimiz ve BoNT/A enjeksiyonlarını tekrarladığımız hastalarımızda birinci ile ikinci uygulamadaki MIDAS skorları arasındaki fark ise %61,1 birinci ile üçüncü uygulamadaki skorlar arasındaki fark ise %65,72 olarak bulunmuştur. (*Nöropsikiyatri Arşivi 2013; 50 Özel Sayı 1: S36-S40*)

**Anahtar kelimeler:** Botulinum toksin, kronik migren, baş ağrısı

**Çıkar çatışması:** Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

## Introduction

In the last two decades, applications of Botulinum toxin (boNT) have increased in clinical medicine. This toxin is especially used widely in treatment of movement disorders, spasticity and syndromes characterized with autonomic hyperactivity (1). In the last ten years, information related with the efficiency of BoNT in treatment of migraine started to accumulate. We aimed to review use of BoNT in episodic and chronic migraine and the studies performed on this issue.

### The Mechanism of Action of Botulinum Toxin

BoNT inhibits release of acetylcholine from the presynaptic vesicles in the neuromuscular junction. Thus, it leads to dose-dependent and reversible muscular paralysis (2). The effect reaches the maximum level 2 weeks after application. Axonal sprouting which develops 2-4 months later ends the effect related with the toxin (2, 3). Neuromuscular conduction returns, but local muscle

paralysis can not fully explain the pain reliever characteristic of BoNT. It is thought that the toxin inhibits peripheral sensitization of the nociceptive fibers and thus decreases central sensitization (4). In many animal and human studies, BoNT/A was shown to inhibit glutamate A, calcitonin gene-related peptide and substance P which are released from activated sensory nerve fibers and which are important mediators of inflammatory pain (5, 6, 7, 8, 9, 10). It is thought that inhibition of these neurotransmitters prevent neurogenic inflammation and peripheral sensitization. As a result of this, pain signals reaching from the periphery to the central nervous system are decreased. Thus, BoNT/A indirectly blocks central sensitization observed in migraine and other painful conditions.

### Botulinum Toxin Types

BoNT is the exotoxin of Clostridium Botulinum which is an anaerobic bacteria and only A and B types among the 7 serotypes of the toxin (A-G) are used in clinical practice. A type of BoNT (BoNT/A) has 4 subgroups. These include onabotulinumtoxin/A (

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Botox®), abobotulinumtoxin/A (Dysport®), incobotulinumtoxin/A (Xeomin®) and Prosigne® which is produced in China. B type (BoNT/B) which is the type of BoNT found in the market is rimabotulinumtoxin B (Myobloc® or Neurobloc®). Currently, Botox® and Dysport® are found in Turkey.

### Episodic Migraine

Many randomized controlled studies have been conducted to evaluate the efficiency and tolerability of BoNT/A in prophylaxis of episodic migraine. However, difficulties have been experienced in conducting these studies under ideal "blind" conditions because of the effect of paralysing the muscles especially when administered to the frontal muscles. Saper JR et al. injected 25 U (units) BoNT/A into the frontal and temporal muscles in a class 1 study in which BoNT/A was compared with placebo in 232 individuals with a pain frequency of 4-8 times a month. At the first and 3rd months, a marked improvement was found in the frequency, severity and time of pain in both groups and no statistically significant difference was found between the two groups in terms of these parameters (11). In another class 1 study, the efficiency and safety of BoNT/A was investigated in 418 patients with a pain frequency of 4-8 times a month. 1 month and 4 months after injection, it was noted that the frequency of pain decreased compared to the baseline in BoNT/A and placebo groups and no significant difference was found between the two groups (12). In another study, 369 patients who had at least 4 attacks a month and/or less than 15 painful days a month were divided into two groups as responsive to placebo and unresponsive to placebo at the end of 30-day placebo initiation period and these two groups were divided into three treatment groups administered with 90-day intervals. The total dose of BoNT/A was adjusted as 110 U, 260 U and placebo. In the group who were unresponsive to placebo, it was observed that the frequency of migraine attacks decreased on the 180th day both in the patients who received BoNT/A and in the patients who received placebo, but there was no statistically significant difference between the groups (13). In a similar 11-month study performed by Relja et al., the safety and efficiency of BoNT/A was evaluated in 495 patients. In this study, BoNT/A at doses of 225, 150 and 75 U and placebo were used. In all treatment groups, regression in the attacks were observed without any marked difference. No difference in favour of BoNT/A was observed (14).

In a class 2 study performed by Silberstein et al. which lasted for 4 months, the clinical effect of BoNT/A in episodic migraine was investigated by administering doses of 25 and 75 U into the glabella and frontal muscles. In the 25 U group, a marked regression in the number and severity of the attacks and a reduction in analgesic usage and vomiting were observed compared to the placebo group, whereas no significant improvement was observed in the 75 U group compared to the placebo group and it was reported that more side effects occurred (15). The investigators related the lower success rate in the high-dose group with the low number of attacks during the follow-up period compared to the low-dose group.

Evers et al. compared two different doses of BoNT/A (6 U and 100 U) with placebo. They reported that BoNT/A and placebo

administrations into the frontal and neck muscles caused to a reduction in the frequency of attacks and the number of painful days at the end of three months compared to the baseline and no significant difference was found between the two groups (16).

In a study in which the effects of BoNT/A, divalproex and placebo in episodic and chronic migraine were compared, it was observed that the frequency and severity of pain and disability caused by pain decreased in both groups compared to placebo and no significant difference was observed between the two groups (17).

### Chronic Migraine

Chronic migraine is a disease which is observed in 1,3-2,4% of the community and affects the performance in both occupational life and private life (18). The prevalence of chronic migraine in Turkey is 23% (19). A diagnosis of chronic migraine is made by presence of headache more than 15 days a month for 3 months and the finding that the pain meets the diagnostic criteria of migraine on at least 8 days a month and gives response to migraine-specific therapies (20). The most common reason of primary chronic daily headache is chronic migraine and the risk of development of drug abuse (used to control pain) headache is high in these patients.

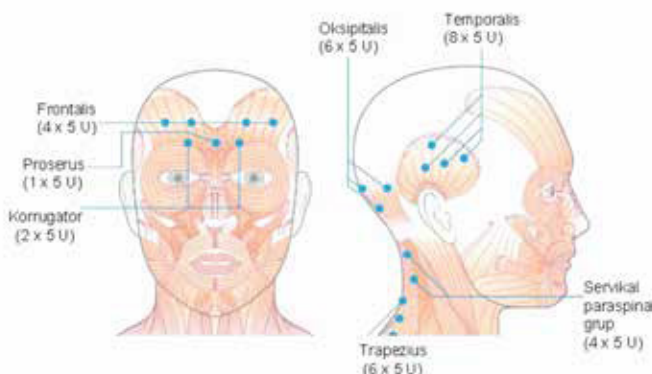
In studies in which BoNT/A was administered at different doses and in different injection sites in prophylactic treatment of chronic daily headache, the efficiency of BoNT/A in treatment of chronic migraine was demonstrated (15, 21, 22, 23). In the first one of the three class 1 studies related with chronic migraine, Freitag et al. administered 100 U BoNT/A at a stable dose (n=21) and placebo (n=20) in stable injection sites (glabella, frontalis, temporal, trapezius, suboccipital) in chronic migraine patients in a double-blind, placebo controlled fashion. In this study, drug abuse headache was excluded. The number of migraine attacks

**Table 1.** Comparative data (p value) of the patients who were given Botulinum toxin A and placebo in PREEMPT 1 (25) and PREEMPT 2 (26) studies and a common study comparing these two studies (27) are shown.

Parameters	PREEMPT 1 (p)	PREEMPT2 (p)	Common study (p)
Day frequency	0.006	<0.001	<0.001
Attack frequency	0.34	<0.003	<0.001
With migraine			
Day frequency	0.002	<0.001	<0.001
Moderate-severe			
Frequency of day with headache	0.004	<0.001	<0.001
Headache Impact			
Test score	0.001	<0.001	<0.001
During the days with headache			
Total hours with headache	<0.001	<0.001	<0.001
Frequency of receiving triptane	0.23	<0.001	<0.001
P<0.05			

( $p<0.01$ ), the number of days with headache ( $p=0.041$ , at the 4<sup>th</sup> week;  $p=0.046$  at the 16<sup>th</sup> week) and the headache index ( $p=0.003$ , at the 16<sup>th</sup> week) were assessed. At the end of the study, BoNT/A was found to be statistically significantly superior compared to placebo (24). Two multi-center, phase 3, class 3 studies in which 1384 chronic migraine patients were compared with BoNT/A and placebo groups 24 weeks of which were double-blind and 32 weeks of which were open (PREEMPT 1, PREEMPT 2) were published in 2010 and it was confirmed that BoNT/A was an efficient, safe and well-tolerated prophylactic agent in treatment of chronic migraine as a result of these two studies (25,26). In these studies in which patients with drug abuse headache were also included, 155 U BoNT/A was administered in all patients in the 31 injection sites in the muscles of the head and neck. Additionally, 40 U BoNT/A was injected optionally into 8 injection sites in three head and neck muscles if the patient had tender and painful regions. Thus, each patient received a minimum dose of 155 U and a maximum dose of 195 U BoNT/A. The number of headache attacks was evaluated primarily in PREEMPT 1 and the number of days with headache was evaluated in PREEMPT 2 at the end of the 24-week period. In both studies, the frequency of days with headache was found to be statistically significantly decreased compared to placebo ( $p=0.006$ ;  $p<0.01$ ). Another study which evaluated the data of PREEMPT 1&2 studies together was published in 2010 (Table 1) (27). Following these studies BoNT/A was approved for treatment of chronic migraine in USA and UK in 2010 and in Turkey in 2011.

Studies have shown that chronic migraine patients tolerate BoNT/A well and the rate of discontinuation of treatment due to side effects is low (%1.4-3.8) (21, 27, 28). With the other prophylactic agents the rate of discontinuation due to side effects has been reported to be 12.7% (28). In another study, it was demonstrated that 75% of the patients ( $n=729$ ) discontinued treatment or changed the drug he/she was using for prophylaxis one year later (29). In the light of all this information, the frequency of discontinuation of prophylactic treatment for chronic migraine because of side effects renders BoNT/A an attractive, alternative treatment option.



**Figure 1.** Constant site, constant dose injection scheme applied in PREEMPT studies  
Blumenfeld A et al. Lancet 2010.

An alternative point of view and criticism related with use of BoNT/A in chronic migraine came from Solomon S (30). It was stated that the placebo effect of BoNT/A was related with administration of injection and the patients could differentiate BoNT/A and placebo according to presence of creases on the forehead. In addition, three randomized controlled studies (21, 25, 26) which evaluated the efficiency of BoNT/A in chronic daily headache demonstrated that BoNT/A was not superior to placebo.

#### Injection Techniques and Experience of our Clinic

BoNT products have different dosage, safety and efficiency properties. Therefore, the doses are not equivalent among these products and calculations should be done separately for each product (31). It is recommended that injections be administered into the intramuscular area rather than the intradermal area (32). Injections into the periostium, eyelid and superficial vessels should be avoided. Injections administered into the forehead should be bilateral and symmetrical in order not to cause to a negative cosmetic effect in the patient.

Two techniques have been accepted in injection: "Follow the pain" and "fixed dose, fixed site". Many centers prefer to combine these two techniques. The injection is administered into the frontal, temporal and occipital areas. There are views which mention the benefits of injections in the trigger points found in the muscles of the back with palpation in addition to the present injection sites with the condition of not creating excessive weakness in the muscles of the neck (33). The benefits of doses of 150-225 U of BoNT/A in each injection in chronic daily headache have been demonstrated (21, 22). An important point which should be noted is the fact that injections administered in a period shorter than 3 months and at high doses may lead to development of antibody and loss of efficiency (34).

In PREEMPT 1&2 studies related with chronic migraine, 155 U BoNT/A is injected at a consistent dose in 31 sites in 7 specific head and neck muscles. Following the pain the physician injects an additional dose of 40 U BoNT/A in the temporal, occipital and trapezius muscles if necessary (a total of 195 U BoNT/A in 39 injection sites). We apply PREEMPT study protocol in our clinic in Acibadem Maslak Hospital Neurology Division. Accordingly, 100 U BoNT/A in a vial is mixed with 2 cc normal saline and placed in 1 ml injectors as 5 U/0.1 ml and 0.1 ml (5U) BoNT/A is injected into each injection site. Corrugator, proserus, frontalis and temporal muscle injections are administered when the patient is in the supine position. Occipital, cervical, paraspinal and trapezius muscle injections are administered when the patient is in the sitting position (Figure 1).

#### Injection Administration Sites

##### Corrugator and Proserus

Injection is started in the glabellar region. Since the muscles in this region are superficial, superficial injection is sufficient in order not to harm the periostium. While administering bilateral 5 U BoNT/A injection into the corrugator muscles 1.5 cm (one finger) superior to the medial superior corner of the orbita, the tip of the

needle is directed upwards to avoid a potential ptosis of the eyelid. Injection into the procerus muscle is administered in the middle of both corrugator muscles 1.5 cm superior to the medial superior corner of the orbita.

### Frontalis

There are a total of four injection sites in the frontalis muscle. For medial injection sites the region 1.5 cm superior to the corrugator muscle is used and for lateral injection 1.5 cm lateral of this site is used. Since the frontal muscle is also superficial, the injection is recommended to be administered superficially in order not to harm the periostum.

### Temporalis

A total of 8 injections are administered into bilateral temporal muscles. Firstly, the patient is asked to clench his/her teeth and the temporalis muscle is palpated. The first injection is administered into the anterior part of the temporalis muscle. The second injection is administered into the medial part of the muscle 0.5 cm superior and 1.5 cm posterior to the first injection site. The third injection site is localized 1.5 cm posterior to the second injection site. The fourth site is in the medial side of the muscle vertical to and 1.5 cm below the second injection site.

### Occipitalis

Before injection the occipital region is palpated in terms of sensitivity to pain. A total of 6 injections are administered into the right and left occipital muscles. The first injection is administered above the occipital protuberance line and approximately 1 cm right/left to the external occipital protuberance. The second injection is localized approximately 1 cm above and 1 cm right/left to the first injection site. The third injection is localized 1 cm above and 1 cm medial to the second injection sites.

### Paraspinal Muscle Group

It is recommended not to administer very deep injections during cervical paraspinal muscle injection in terms of potential weakness which may develop in the muscles of the neck. The first injection is administered 3-5 cm inferior to the occipital protuberance, in the lateral side of the midline. The second injection is administered 1 cm lateral and superior to the first injection (diagonally from the first injection to the ear). A total of 4 injection sites are found in the right and left side.

### Trapezius

Finally, the trapezius muscle is palpated in terms of pain and injection is administered into the superior part of the muscle. The muscle is imaginatively divided into three parts and the first injection is administered into the lateral part of the muscle. The second injection is administered into the middle part of the muscle in a little more medial region and the last injection is administered into the superior and medial area of the muscle. Injection into the infero-medial part of the trapezius muscle is avoided in order not to cause to weakness in the muscles of the neck.

If this application is performed by an experienced physician, it lasts 10 minutes at most. The patients are observed for 10-15 minutes after treatment. They are advised not to massage the injection sites for 24 hours and informed that the swelling in their

foreheads will recover in 2 hours. It is reported that the efficiency of this treatment will start in about 10 days and they can use drugs for treatment of acute attacks if they have migraine attacks during this period. The recommended time for a new BoNT/A injection is 12 weeks. It is recommended that the patients are followed up with an headache diary during this period.

In a pilot study which we started in our clinic and which is still ongoing, the therapeutic effect of BoNT/A on headache was evaluated in 30 patients with a diagnosis of migraine (28 women and 2 men) with a mean age of  $39.5 \pm 7.8$  years 10 of whom had a history of drug abuse. 155 U BoNT/A was injected in the patients three times with 12-week intervals in accordance with PREEMPT protocol. Migraine disability assessment (MIDAS) scores were determined before the injection and after each injection. MIDAS which was translated to Turkish and for which a validity and reliability study was conducted is a test which determines migraine disability in all areas of activity in the last 3 months (35).

At the first visit, the mean MIDAS value of the patients was found to be  $59.5 \pm 24.3$  (n=30). At the 12th week, the mean MIDAS score was found to be  $23 \pm 20.6$  (n=12) and injections were repeated. At the 24th week, the mean MIDAS score was found to be  $20.4 \pm 20.1$  (n=5). In our patients, the difference between the 1st and 2nd MIDAS scores was found to be 61.1% and the difference between the 1st and 3rd MIDAS scores was found to be 65.72%. In our small patient group, improvement in MIDAS scores was observed beginning from the first injection and a marked regression was observed in the severity and frequency of pain. The data of our pilot study suggested that BoNT/A is an efficient and safe treatment option in migraine prophylaxis similar to the results of PREEMPT study. Therefore, it should be kept in mind that BoNT/A is an important and efficient option in patients with a diagnosis of chronic migraine who do not respond to current prophylactic therapies and whose daily life activities are affected negatively because of the frequency and severity of pain.

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